Predictors of Short-term Clinical Response to Cardiac Resynchronization Therapy

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Short Title: Predictors of CRT Clinical Response

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Abstract (Word Count: 166)

Aims: Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients with symptomatic heart failure (HF) and QRS prolongation but there is uncertainty about which patient characteristics predict short-term clinical response.

Methods and Results: In an individual patient meta-analysis of three double-blind, randomized trials, Clinical Composite Score (CCS) at 6 months was compared in patients assigned to CRT programmed on compared to off. Treatment-covariate interactions were assessed to measure likelihood of improved CCS at 6 months.

MIRACLE, MIRACLE ICD, and REVERSE trials contributed data for this analysis (n=1591). Multivariable modelling identified QRS duration and left ventricular ejection fraction (LVEF) as predictors of CRT clinical response ($p<0.05$). The odds ratio for a better CCS score at 6 months increased by 3.7% for every 1% decrease in LVEF for patients assigned to CRT-on compared to CRT-off, and was greatest when QRS duration was between 160 ms and 180 ms.

Conclusions: In symptomatic chronic heart failure patients (NYHAII-IV), longer QRS duration and lower LVEF independently predict early clinical response to CRT.

Key Words: Cardiac resynchronization therapy, heart failure, symptoms

ABBREVIATIONS

CCS: Clinical composite score

CRT: Cardiac resynchronization therapy

HF: Heart failure

HFH: Heart failure hospitalization

ICD: Implantable cardioverter defibrillator

IPD: Individual Patient Data

LBBB: Left bundle branch block

LOCF: Last observation carried forward

LVEF: Left ventricular ejection fraction

NYHA: New York Heart Association

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established therapy for patients with heart failure (HF) with a reduced left ventricular ejection fraction (LVEF) and electrical dyssynchrony (1-3). Prospective randomized trials of CRT have consistently demonstrated reductions in heart failure related hospitalization (HFH) and mortality rate among patients with a broad spectrum of symptomatic HF (4-7). CRT can also improve symptoms or, in those with few or no symptoms, prevent deterioration. Although CRT makes a valuable contribution to HF management, it is relatively expensive and associated with complications. Additionally, not all HF patients improve with CRT, which highlights the need for better ways to predict who will benefit from this therapy within the first months of treatment when recommending CRT to the patient.

We previously identified QRS duration as the only significant predictor of morbidity and mortality benefit after adjusting for covariates (5). Although morbidity and mortality are "hard" endpoints in clinical trials, they identify only patients who worsen. For patients with a disease that is likely to progress, such as HF, prevention of deterioration may be just as important (8). The present analyses pooled patient-level data from three randomized trials to assess baseline predictors for short-term clinical response to CRT, defined either as an improvement or maintenance of HF status depending on symptom severity at baseline.

METHODS

Individual patient data (IPD) from three randomized controlled trials sponsored by one manufacturer (Medtronic plc, Minneapolis, USA) comparing CRT programmed on or off were pooled for this analysis. The studies were selected because they were double-blind and had the Clinical Composite Score (CCS) as a primary (REVERSE) or secondary (MIRACLE and

MIRACLE ICD) outcome. All included studies complied with the *Declaration of Helsinki*, the locally appointed ethics committees approved the research protocol for each study, and all patients provided written informed consent. Data were pooled for 1591 patients comparing either CRT with back-up pacing (MIRACLE (9), REVERSE (10, 11)) or CRT-D with ICD (REVERSE (10, 11), MIRACLE-ICD (12, 13)). In the control arm backup right ventricular pacing (VVI) was programmed to allow for intrinsic rhythm as much as possible and was VVI 30 in MIRACLE (9) and VVI 35 in MIRACLEICD (12,13) and VVI 35 REVERSE (10,11). In all trials, patients and endpoint assessment study personnel were blinded to treatment. In order to create a more homogeneous population, patients in New York Heart Association (NYHA) class I (107 patients from REVERSE) were excluded. The remaining patients were in NYHA III/IV (MIRACLE/MIRACLE ICD) or NYHA II (MIRACLE ICD/REVERSE). All patients were on guideline-recommended pharmacological therapy for HF before being randomized.

The following pre-specified baseline variables were included in the analyses: age, sex, NYHA class, etiology, QRS morphology, QRS duration, left ventricular ejection fraction (LVEF), and systolic blood pressure. Core-laboratory values were used for ECG measurements in REVERSE and for echocardiographic assessment of LVEF in all studies.

Short-term (6 months) response in Clinical composite Score (CCS)

Our outcome for this analysis was the CCS at 6 months (14) developed and used to assess HF patients in many CRT trials (13-17). The CCS classifies patients as *Worsened, Unchanged*, or *Improved* based upon mortality, HF hospitalization, cross-over from assigned randomization, NYHA class, and the patient's own global assessment of their HF state. The global assessment uses seven response options: markedly improved; moderately improved; mild improvement; no change; slightly worse; moderately worse; or markedly worse to define whether overall status

has changed and, if so, in which direction and magnitude compared to baseline. Markedly or moderately improved was considered as a positive response to treatment assignment, markedly or moderately worse as a negative response, and mildly worse or improved or unchanged was judged as no change with assigned treatment. Only in the REVERSE trial were both *Improved* and *Unchanged* regarded as a positive response to treatment since this study included patients in mild HF and thus hypothesized prevention of disease progression with CRT.

Based on all components of the CCS, patients were classified as *Worsened* if a) they died or were hospitalized for worsening HF, b) crossed over to the alternate treatment, or permanently discontinued double-blind treatment due to worsening HF, or c) had a worsening in NYHA functional class or reported a moderate or marked worsening of HF symptoms. Patients were classified as *Improved* if they did not fulfill the criteria for *Worsened* and had an improvement in NYHA functional class, or had a moderate or marked improvement in global assessment, or both. Patients who were neither *Worsened* nor *Improved* were classified as *Unchanged*.

The CCS thus leverages objective measures of death and HFH in combination with subjective measures of NYHA functional class and global assessment. Importantly, CCS accounts for discontinuation of therapy due to clinical deterioration. A hierarchical model was used to identify whether the subject's status *Improved, Worsened,* or is *Unchanged* , placing priority on death, HFH, crossovers, then patient subjective measures. CCS was a last-observation-carried-forward (LOCF) metric, and so was available at 6 months for all patients. Inclusion of patients for analysis of short-term response was dependent on whether all baseline characteristics pre-specified for this analysis were available.

Statistics

Statistical analyses were conducted using the intention-to-treat principle and included patients who failed to receive their assigned treatment (5). Continuously distributed data are shown as both mean and standard deviation and median, inter-quartile range, and full range. Categorical data are shown as percentages. A cumulative logits model was used to assess early response due to the tripartite nature of the CCS. This model included main effects of the covariates defined above as well as corresponding interaction effects with CRT therapy, and simultaneously evaluated how these covariates impacted the likelihood of an Improved score at 6 months as well as the likelihood of an Improved/Unchanged score at 6 months. Quantitative variables (age, QRS duration, LVEF, systolic blood pressure) were treated as continuous variables in the models. Patients in NYHA class III were enrolled in all studies except REVERSE and served as the default for calculating odds ratios, the primary metric of comparison. The odds ratio reflected the odds of superior (e.g. *Improved*/*Unchanged*) CCS among patients with a characteristic or therapy (e.g. with CRT, with NYHA II) compared to those without it. Scores above 1 showed evidence of greater likelihood of superior CCS scores among patients having the characteristic/therapy of interest. Backwards elimination was applied for final model selection.

Estimated Relative Risk (referred to hereafter as Relative Benefit) denoting the ratio of the estimated probability of a CCS score of *Improved* with CRT over the corresponding probability without CRT was plotted based on modeling results for subgroups defined by significant main effects, with a value over 1 indicative of CRT benefit. Plots were generated for subgroups thought to be most representative of the individual MIRACLE, MIRACLE-ICD, and REVERSE populations but also indicative of contemporary treatment patterns such as beta-blocker usage which is higher to date than at the time when the studies were carried out.

RESULTS

Of 1599 patients eligible for this analysis1591 had sufficient baseline data to be included (882 in the CRT group and 717 in the Control group), **(Table 1)**. The two cohorts were similar with regard to concomitant ICD therapy, age, gender, LVEF, QRS duration, and blood pressure. In the CRT group, there were slightly more patients in NYHA II and more patients were on a beta blockers, due to the 2:1 randomization scheme employed in REVERSE which was contrary to the 1:1 assignment in MIRACLE and MIRACLE ICD. Only a few patients in REVERSE received a CRT-P device; therefore, amongst NYHA II patients, the comparison was predominantly CRT-D versus ICD only. Regarding HF medication, ACE inhibitors or Angiotensin receptor II blockers were given in 91, 93 and 97% in the MIRACLE, MIRACLE ICD and REVERSE patients respectively. Beta-blockers were given in 95% of REVERSE patients compared to 56 and 61% in the MIRACLE and MIRACLE ICD trials, respectively. LVEF was on the average 24.6% and QRS width 161 ms.

The breakdown of *Worsened*, *Unchanged*, and *Improved* among CRT patients was 16%, 24%, and 60%, respectively; among Control patients the corresponding breakdown was 26%, 33%, 41% **(Table 2)**. For many patients in both the CRT and Control arms, *Improved* scores were due to both NYHA and Global Assessment improvement (29% and 17%, respectively). *Worsened* CCS among CRT and Control patients was most commonly due to HFH (7% and 12%, respectively).

CRT (ON vs OFF), ICD therapy/indication (Yes/No), NYHA II symptoms, LBBB, LVEF, and beta blocker therapy at enrollment were found to each significantly affect a subject's odds of a better CCS at 6 months when accounting for other predictors **(Table 3)**. However, the

interaction effect for CRT was only significant with LVEF (p=0.0126) and with baseline QRS duration. The nature of the interaction effect of QRS duration with CRT was curvilinear (p=0.0005 and p=0.0026 for linear and quadratic interaction terms, respectively).

CRT exerted a greater benefit in patients with lower ejection fractions and longer QRS durations and was greatest when QRS duration was between 160 ms and 180 ms **(Figure 1)**. CRT benefit (odds ratio >1) was consistent for LVEF $\geq$19% only when QRS duration was $\geq$140 ms **(Figure 1)**. However, for LVEF <19% (n=347), the estimated odds ratio exceeded 1 regardless of QRS duration, exceeding an estimated odds ratio of 4 for some QRS durations; in other words, the odds for being *Improved* at 6 months was 4 times higher with rather than without CRT in this subset of patients with severe HF disease state. There were 63 patients (4% of the cohort) with an LVEF < 19% and a QRS duration < 140 ms.

For patients in NYHA III/IV with LBBB and on beta blockers with or without an ICD, the relative benefit of CRT was as high as 2.4 **(Figure 2A, 3A)**. In addition, patients could also improve if CRT was not programmed on; the probability of this happening was similar regardless of QRS duration but was less likely in patients with a lower LVEF **(Figure 2B, 3B)**. Among CRT patients the probability of benefit decreased at lower LVEF, but not as much as in patients who did not receive CRT pacing. For CRT patients, the probability for benefit increased with QRS duration and leveled off at approximately 170 ms **(Figure 2C, 3C)**.

For patients in NYHA II, almost all of whom had an ICD, the estimated relative benefit of an *Improved* CCS at 6 months with CRT was similar. Broadening the definition of success in this group to include *Improved* or *Unchanged* resulted in a smaller relative benefit **(Figure 4A)** than that for *Improved* alone, because of the high probability of patients being *Unchanged* even if CRT was programmed off **(Figure 4B)** and thus the smaller relative difference with that of the

CRT arm **(Figure 4C)**. However, the estimated relative benefit was still between 1.1 and 1.4 over much of the range of LVEF and QRS durations **(Figure 4A)**, suggestive of a 10 - 40% increase in likelihood of a 6 month CCS of *Improved*/*Unchanged* with CRT.

DISCUSSION

This IPD meta-analysis of double-blind randomized trials confirms that CRT improves a composite of symptoms and outcome by six months and that patients with a lower LVEF and a longer QRS duration are more likely to benefit. After adjusting for confounding (interacting) variables, which is not possible with a conventional meta-analysis, only QRS duration and LVEF were significant predictors of clinical response to CRT. These findings build on our previous observations in a similar IPD meta-analysis that QRS duration was the only independent predictor of the effect of CRT on morbidity and mortality but focus on the short term response which is also important for the patient (5).

Previous studies have indicated that LBBB is a univariate predictor of response to CRT but not always a significant predictor after adjusting for covariates (15-18). Several subgroup analyses from randomized clinical trials and single-center studies have suggested that patients without LBBB may derive less benefit from CRT (19-23). In MADIT-CRT, there was a trend for increased mortality from CRT in non-LBBB patients despite indications of reverse remodeling (18). However, patients with LBBB have longer QRS durations (mean= 163±19 ms) compared to those without LBBB (mean = 146±15 ms) and are less likely to have ischemic heart disease (18). After adjusting for covariates, QRS morphology may no longer be a statistically significant predictor of the response to CRT but might nonetheless be an important clinical substrate. Clearly, this is a controversial area that requires more evidence and thought.

Many analyses exploring predictors of the response to CRT lack a control group. These analyses can predict the outcome with a therapy but not the response to it (24). In order to know what the response to a therapy is, the response of similar patients without the intervention must be known, preferably from a double-blind randomized trial. In our analysis the probability of an improvement *without* CRT was consistent across QRS duration but decreased in patients with a lower LVEF. Device therapy including CRT has a placebo-effect (11, 12, 25) particularly over a short term time period (26). Patients will also improve in response to changes in lifestyle and pharmacological therapy. This analysis shows the importance of having a control group to ensure that the effects of the intervention can be distinguished from the natural history of the disease. In this analysis heart failure hospitalizations were clearly the most common reason for patients worsening in both study groups but were especially pronounced in the CRT off group.

In our study several baseline variables (ICD therapy, NYHA II symptoms, presence/history of LBBB, LVEF, and beta blocker usage at baseline) were found to significantly affect a patient's odds of improved clinical response at 6 months. However, when examining the interaction effect for CRT, only QRS duration and LVEF were significant. This suggests that some variables such as these influence the progression of HF whether or not the patient receives CRT. Our finding contrasts with previous studies which suggest that patient characteristics such as older age, male sex, RBBB, and ischemic etiology are linked to less benefit from CRT (21, 24, 27, 28). However, these studies either lack a control group or statistical power. We used individual patient data rather than aggregated data, and studied the interaction between QRS duration and morphology as well as interaction with CRT therapy. Our results thus, represent a much more robust analysis than other meta-analyses (19-23).

Our results may contribute information to new guidelines. Currently, CRT is most strongly recommended for symptomatic HF patients with an LVEF ≤30 or 35% with a QRS duration ≥150 ms and LBBB, with a weaker recommendation for patients without LBBB and in less prolonged QRS (120 ms or 130 ms) (29-31). The most recent guidelines from the European Society of Cardiology (32) stress the importance of not implanting CRT in patients with QRS < 130 ms based on the ECHO CRT study (33) since CRT was linked to excess mortality in this study. Our new findings, focusing on the short-term clinical response to CRT suggest clinical benefit from CRT in patients with QRS ≥140 irrespective of bundle branch morphology and that patients with a lower LVEF are more likely to benefit from CRT even at a modest QRS prolongation of QRS duration < 140 ms. In our meta-analysis such patients were few and represent a small subgroup making it difficult to draw solid conclusions. In contrast, in the ECHO CRT only patients with QRS < 130 ms were included.

For the patient it is relevant to get the treating physician's view on what to expect from CRT when making a decision on whether to be implanted or not. Symptomatic improvement over the first months of treatment may be important for the patient irrespective of any long term benefits on morbidity and mortality. We clearly show strong evidence for symptomatic improvements after 6 months of CRT therapy by the endpoint in this meta-analysis – the CCS. This endpoint has several advantages. It includes components of symptomatic improvement such as NYHA class estimated by study professionals and global assessment questions on symptoms answered by the patients. A further strength of CCS is that, unlike other endpoints, every patient contributes to the analysis through the tested duration. A component of the CCS is NYHA class, which itself has been used as an endpoint in CRT trials (9). Our results are strengthened by the fact that all studies included in this analysis assessed NYHA class in a blinded manner.

Our analysis also puts the response rate to CRT into perspective by relating it to important baselines covariates. Defining patient response across multiple subgroups is important for translating findings from a clinical trial to a "real-world" HF population. Careful patient selection is essential in obtaining the most benefit from existing CRT technologies. While different strategies to improve response are advancing, such as lead placement, imaging, and device programming, our analysis indicates that these approaches need to show that they are superior to selection by both QRS duration and LVEF. Although morbidity and mortality are important gold-standards for the assessment of many treatments for heart failure, they have weaknesses. They may not be the most important goals of therapy either for those who have very severe or very mild symptoms. For the former group, relief of symptoms may be more important. For the latter group, morbidity and mortality may already be low and the main medium-term goal may be delaying or preventing the progression of disease. Indeed in our study the proportion worsening was more common in the control group and was driven by heart failure hospitalizations whereas improvement was more common in the CRT group and was driven by patient´s global assessment or NYHA class. The CCS balances a clinical outcome that is meaningful to both patients and clinicians with a robust measurement that increases the feasibility of conducting trials of sufficient size and duration to identify important effects.

Limitations

An important limitation of this analysis was the restriction to those studies in which we had access to individual patient data. As in all clinical trials, care should be taken in interpreting data from subgroups and in extrapolating data gathered from patients selected for a clinical trial to the wider patient population that might be considered for CRT. However, these analyses

included a large patient population with heterogeneity in symptom severity and intervention (ICD vs. CRT). Results of our analysis indicated these background differences did not influence the response to CRT. Choice of baseline covariates to evaluate was predefined, and not based on minimum sample size requirements for subgroups; it is not known how or whether this affected analysis results.

Conclusions

In a meta-analysis of double-blind randomized controlled trials, longer QRS duration and lower LVEF predict a favorable response to CRT defined as improvement at 6 months in Clinical Composite Score; a measure driven mainly by symptom status.

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Authors Contributions: Dr. Linde, Dr. Abraham, Dr. Gold, Dr Daubert, Dr. Tang, Dr. Young, and Dr. Cleland led steering committees and participated in clinical trials that are contributing wholly to this meta-analysis. Dr. Sherfesee conducted the statistical analysis. Dr. Linde drafted and all authors critically revised and approved the manuscript. All authors agree to be accountable for all aspects of the work.

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Figure Legends

Figure 1: Estimated Odds Ratio of CRT programmed on versus off on 6 month CCS by QRS Duration and by LVEF. Odds ratio increases as LVEF decreases, and for each LVEF value is greatest when QRS duration is between 160 and 180 ms.

Figure 2: Estimated Probability of an Improved CCS at 6 Months (ICD, Beta Blockers, LBBB, NYHA III/IV). Estimated Relative Benefit **(2A)** and probability of 6 Month CCS score of Improved for patients with CRT programmed off **(2B)** and CRT programmed on **(2C)** for patients in NYHA III/IV with an ICD, LBBB and on Beta Blockers. Relative benefit scores **(2A)** over 1 denote greater likelihood of *Improved* scores with CRT. Y-axis for **2B** and **2C** denote probability (0.25 = 25%)

Figure 3: Estimated Probability of an Improved CCS at 6 Months (Non-ICD, Beta Blockers, LBBB, NYHA III/IV). Estimated Relative Benefit **(3A)** and probability of 6 Month CCS score of Improved for CRT programmed off **(3B)** and CRT programmed on **(3C)** for patients in NYHA III/IV, without an ICD but with LBBB and on Beta Blockers. Relative benefit scores over 1 denote greater likelihood of *Improved* scores with CRT.

Figure 4: Estimated Probability of an Improved/Unchanged CCS at 6 Months (ICD, Beta Blockers, LBBB, NYHA II). Estimated Relative Benefit **(4A)** and probability of 6 Month CCS score of Improved or Unchanged for CRT programmed off **(4B)** and CRT programmed on **(4C)** for patients in NYHA II with an ICD, LBBB and on Beta Blockers. Relative benefit scores over 1 denote greater likelihood of *Improved*/*Unchanged* scores with CRT.

Table 1: Patient Characteristics

Patient and Study Characteristics	CRT (N=882)	Control (N=717)
Study		
MIRACLE	266 (30.2%)	275 (38.4%)
MIRACLE-ICD	272 (30.8%)	283 (39.5%)
REVERSE	344 (39.0%)	159 (22.2%)
Gender (N, %)		
Male	666 (75.5%)	551 (76.8%)
Female	216 (24.5%)	166 (23.2%)
Concomitant ICD therapy	556 (63.0%)	421 (58.7%)
Age (years at baseline visit)		
Mean ± Standard Deviation	64.1 ± 11.1	64.4 ± 11.2
Median	65.5	66.0
25th Percentile – 75th Percentile	56.9 – 72.1	57.5 – 73.2
Minimum – Maximum	23.0 – 89.0	20.4 – 93.8
Baseline Left Ventricular Ejection Fraction		
Mean ± Standard Deviation	24.7 ± 7.0	24.4 ± 7.0
Median	24.5	24.0
25th Percentile – 75th Percentile	20.0 – 29.1	19.8 – 29.5
Minimum – Maximum	8.9 – 51.6	6.0 – 45.0
N (%) of Patients with LVEF Avail.	881 (99.9%)	717 (100%)
Baseline QRS Duration		
Mean ± Standard Deviation	160.6 ± 23.2	161.6 ± 22.4
Median	160.0	160.0
25th Percentile – 75th Percentile	144 – 176	145 – 176
Minimum – Maximum	93 – 250	80 – 240
N (%) of Patients with QRS Avail.	882 (100%)	717 (100%)
Baseline Supine Systolic BP		
Mean ± Standard Deviation	118.8 ± 18.7	116.8 ± 18.1
Median	118	114
25th Percentile – 75th Percentile	106 – 130	105 – 128
Minimum – Maximum	74 – 205	78 – 183
N (%) of Patients with BP Avail.	880 (99.8%)	712 (99.3%)
Baseline Supine Diastolic BP		
Mean ± Standard Deviation	69.6 ± 10.9	68.7 ± 10.7
Median	70	70
25th Percentile – 75th Percentile	60 – 78	60 – 76
Minimum – Maximum	35 – 112	42 – 110
N (%) of Patients with Measurement	880 (99.8%)	712 (99.3%)
NYHA Classification		
NYHA II	429 (48.6%)	260 (36.3%)
NYHA III	404 (45.8%)	410 (57.2%)
NYHA IV	49 (5.6%)	47 (6.6%)
Morphology		
Left Bundle Branch Block*	639 (72.4%)	509 (71.0%)
Right Bundle Branch Block†	82 (9.3%)	92 (12.8%)
Neither	166 (18.8%)	125 (17.4%)
Ischemic	493 (55.9%)	432 (60.3%)
Beta Blocker Usage at Baseline	654 (74.2%)	465 (64.9%)

*LBBB status not known for some patients

†There were some patients with both a history of LBBB and RBBB; these are counted in both groups

Table 2: CCS Breakdown Among CRT and Control Subjects

CCS Reason	Control (N=717)	CRT (N=882)
Improved N(%)	**297 (41.42)**	**525 (59.52)**
Global Assessment	72 (10.04)	131 (14.85)
NYHA	102 (14.23)	137 (15.53)
NYHA & Global Assessment	123 (17.15)	257 (29.14)
Unchanged N(%)	**236 (32.91)**	**215 (24.38)**
Worsened N(%)	**184 (25.66)**	**142 (16.10)**
Death	37 (5.16)	36 (4.08)
Exit	3 (0.42)	3 (0.34)
Global Assessment	15 (2.09)	10 (1.13)
HFH	83 (11.58)	60 (6.80)
NYHA	33 (4.60)	24 (2.72)
Crossover/Reprogram	13 (1.81)	9 (1.02)

Table 3: Main Modelling Results for Short-Term Response

	Short-term Response at 6 Months	
	Odds Ratio	**P-value**
Main Effects		
ICD Therapy	**0.773**	**0.0253**
CRT Therapy	**0.546**	**0.0382**
Age at Baseline	NS	NS
NYHA II	**1.370**	**0.0090**
NYHA IV	NS	NS
Left Bundle Branch Block	**1.447**	**0.0013**
Ischemic Heart Disease	NS	NS
Gender: Male	NS	NS
Beta Blocker Use at baseline	**1.442**	**0.0010**
Systolic BP at baseline	NS	NS
QRS Duration (linear)	0.990	NS
QRS Duration (quadratic)	1.0001	NS
LVEF (linear)	**1.057**	**<0.0001**
LVEF (quadratic)	NS	NS
Interaction with Effect of CRT		
ICD Therapy	NS	NS
Age at Baseline	NS	NS
NYHA II	NS	NS
NYHA IV	NS	NS
Left Bundle Branch Block	NS	NS
Ischemic Heart Disease	NS	NS
Gender: Male	NS	NS
QRS Duration (linear)	**1.044**	**0.0005**
QRS Duration (quadratic)	**0.9996**	**0.0026**
LVEF (linear)	**0.964**	**0.0126**
LVEF (quadratic)	NS	NS
B-Blocker Use at baseline	NS	NS
Systolic BP at baseline	NS	NS

Items in bold are statistically significant at $p<0.05$

Figure 1:

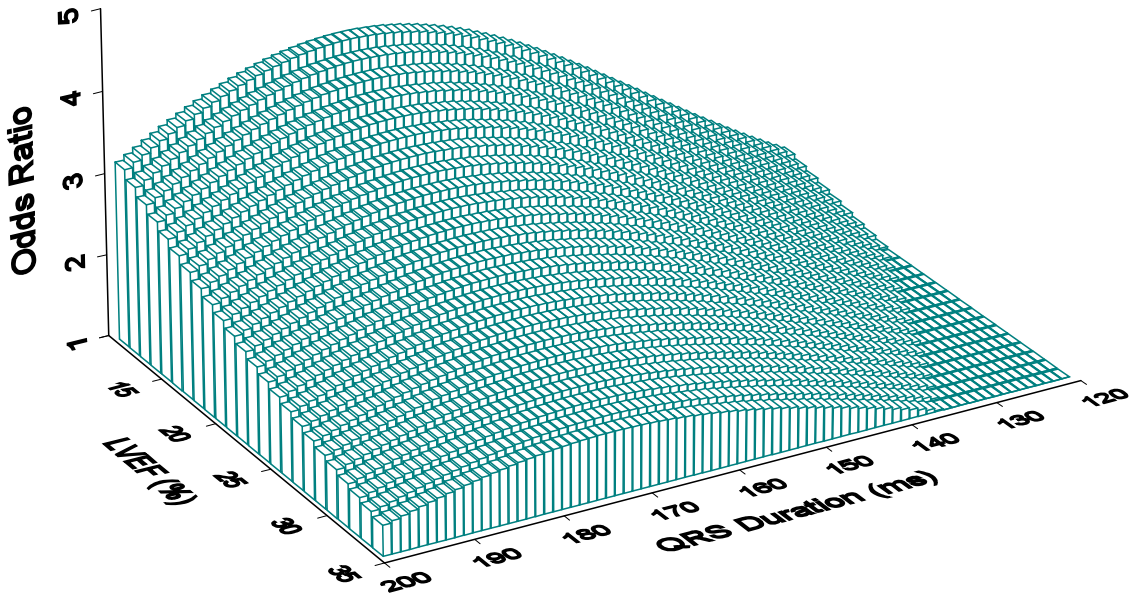
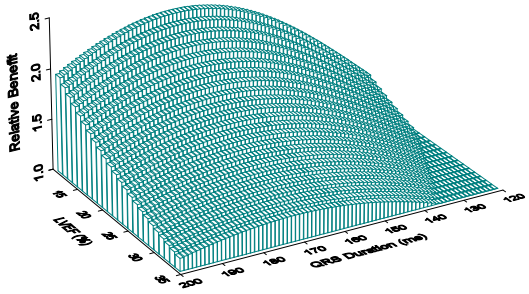

Odds Ratio
1
2
3
4
5
LVEF (%)
15
20
25
30
35
QRS Duration (ms)
200
190
180
170
160
150
140
130
120

Figure 2:

2A:



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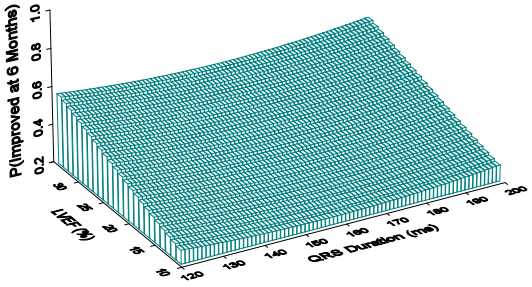

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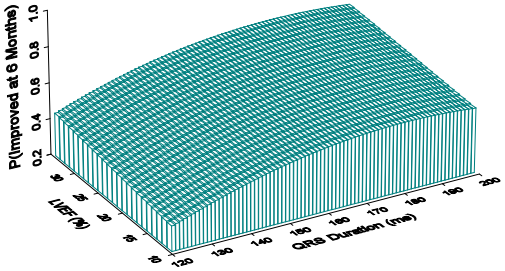

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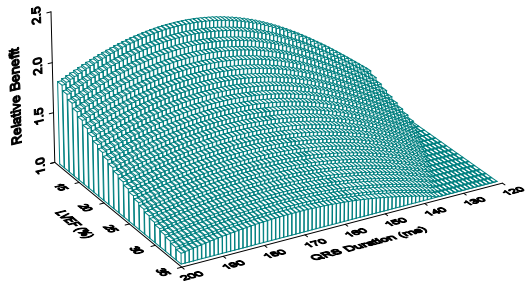
3A:



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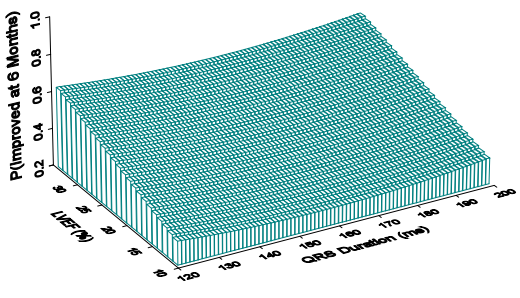

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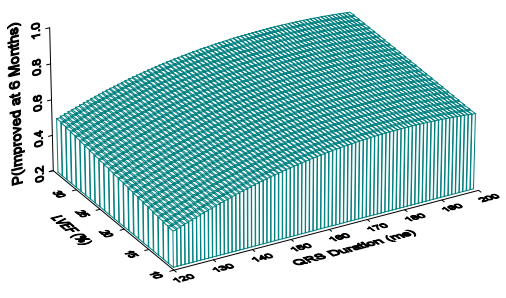
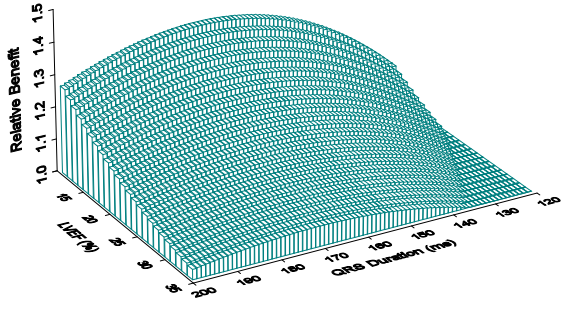


Figure 4:

4A:



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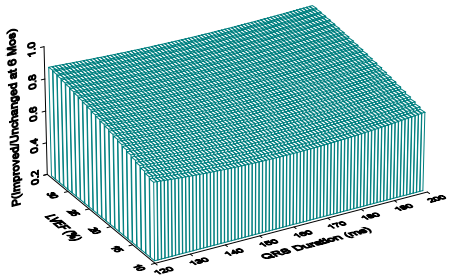

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